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Role of Antibiotic Therapy in Mild Acute Calculus Cholecystitis: A Prospective Randomized Controlled Trial

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Abstract

Background Current recommendations for treating acute calculus cholecystitis include the use of intravenous antibiotics, although these recommendations were never tested scientifically. The aim of this study was to evaluate the role of intravenous antibiotic therapy in patients with mild acute calculus cholecystitis.

Methods In this prospective, randomized controlled trial, 84 patients with a diagnosis of mild acute calculus cholecystitis were randomly assigned to supportive treatment only or supportive treatment with intravenous antibiotic treatment (42 patients in each arm). Patients were followed through their index admission and until delayed laparoscopic cholecystectomy was performed.

Results The two study groups did not differ in their demographic data or in the clinical presentation and disease severity. Analysis was conducted on the intent-to-treat basis. Patients in the intravenous antibiotics arm resumed a liquid diet earlier (1.7 vs. 2.2 days, $p = 0.02$) but did not significantly differ in resumption of regular diet (2.8 vs. 3.2 days, $p = 0.16$) or hospital length of stay (LOS) (3.9 vs. 3.8 days, $p = 0.89$). Patients in the intravenous antibiotics arm had rates of percutaneous cholecystostomy tube placement (12 vs. 5 %, $p = 0.43$), readmissions (19 vs. 13 %, $p = 0.73$), and perioperative course similar to those not receiving antibiotics. The overall hospital LOS, including initial hospitalization and subsequent cholecystectomy, was similar for both groups (5.6 vs. 5.1 days, $p = 0.29$). Eight (19 %) patients in the supportive arm were crossed over to the intravenous antibiotic arm during the index admission.

Conclusions Intravenous antibiotic treatment does not improve the hospital course or early outcome in most of the patients with mild acute calculus cholecystitis.

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Introduction

Cholelithiasis and inflammatory diseases of the biliary tract constitute a major health problem in developed countries. Acute calculus cholecystitis (ACC) is the third major cause of emergency admissions to surgical wards, and its incidence increases with age [1]. An estimated 20 to 25 million adults in the United States are afflicted with gallstones, and population-based statistics showed that 262,411 hospitalizations occurred in the United States during 2000 for ACC [2]. About 750,000 cholecystectomies are performed annually in the United States, of which about 20 % are due to ACC [3].

Acute calculus cholecystitis is defined as acute inflammation of the gallbladder, commonly caused by gallstones impacted in the cystic duct [3, 4]. In most cases, the inflammatory process is initially sterile; however, bactibilia with microorganisms of the Enterobacteriaceae family, enterococci, or more rarely anaerobes occurs in 9 to 72 % of the patients [5–8]. The initial treatment of ACC involves cessation of oral intake, intravenous fluids, and intravenous antibiotics. This protocol has also been advocated and adopted by the Tokyo guidelines for the treatment of acute cholecystitis [9].

Unlike the extensive investigations as to the timing of surgery, the role of antibiotic treatment for ACC lacks a solid evidence basis [10, 11]. Recent recommendations by the Surgical Infection Society and the Infectious Diseases Society of America include intravenous antibiotics as part of the treatment of ACC and rely almost entirely on the Tokyo guidelines [12]. However, the Tokyo guidelines identify patients with mild ACC who may be observed or treated only with oral antimicrobial drugs [9]. Furthermore, the Tokyo guidelines also include treatment with nonsteroidal antiinflammatory drugs (NSAIDs) in this subclass, consistent with the notion that the pathophysiology of ACC is inflammatory rather than infectious [13].

Antibiotic treatment in general, is associated with adverse effects, greater costs, and most importantly unavoidable development of bacterial drug resistance. To date, there have been no randomized trials that assessed the need for antibiotics in patients with ACC. The objective of this study was to evaluate the efficacy and role of intravenous antibiotic therapy in patients with mild ACC and, more specifically, the effect on hospital length of stay and early outcomes. The hypothesis was that antibiotic treatment does not affect the outcomes of this defined group of patients.

Methods

Study design

The reporting of this clinical trial is in accordance with the CONSORT consensus statement [14]. The study protocol of this single institution, randomized, controlled clinical trial was reviewed and approved by the Independent Ethical Committee, Hadassah-Hebrew University Medical Center (IEC, Helsinki Committee, protocol HMO-0364). The study was registered as a clinical trial with NCT identifier NCT00557453.

Patients were enrolled from February 2008 to February 2010 after signing an informed consent form. There were no changes in the study's approved protocol after the trial was initiated, and there were no unexplained discrepancies in randomization or statistical analysis. The primary analysis was intention-to-treat and involved all patients who were randomly assigned to each group.

Participants

Eligible patients who were 18 to 70 years of age and who were hospitalized at the Hadassah-Hebrew University Medical Center, Mount Scopus, with the diagnosis of acute calculus cholecystitis were prospectively enrolled in the study once they met all inclusion criteria. The diagnostic criteria for ACC followed the final version of the Tokyo consensus meeting [15] and included the following: sonographic findings of cholecystolithiasis or sludge, wall thickening $\geq$4 mm, and a positive sonographic Murphy sign. In addition to the sonographic findings, one of the following clinical criteria was required: epigastric or right upper quadrant pain, fever >38.0 °C, or a white blood cell (WBC) count >10,000/mm^3.

Notable exclusion criteria included patients with evidence of moderate or severe ACC, such as fever >39 °C, a palpable inflammatory mass in the right upper quadrant, evidence of peritoneal irritation signs on physical examination, WBC >18,000/mm^3, hemodynamic instability, or multiorgan failure (as defined by the European Society of Intensive Care). Detailed exclusion criteria are presented in Table 1.

Once the diagnosis was made and the patient was determined eligible to be included in the study, participation was offered by one of the department's residents. Detailed consent was obtained for all participants.

Settings and locations

The study was performed at Hadassah-Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel, a university teaching hospital located at the eastern side of Jerusalem that treats both Arabic and Jewish populations from the eastern and western parts of the city, respectively. The estimated annual incidence of patients with ACC admitted through the emergency room is approximately 100 patients per year. In this study, patients admitted through the emergency room were diagnosed and evaluated for inclusion. Once they gave their consent, the patients were admitted to the Department of Surgery for further treatment. The only caregivers involved in the recruitment and treatment of the patients were Department of Surgery staff.

Treatment protocols

Initial treatment of all patients included complete cessation of oral intake and initiation of intravenous fluids. All

Table 1 Exclusion[a] criteria

Age <18 or >70 years
Pregnant female patients
Patients who did not consent
NYHA >3
Steroids or immunosuppressive therapy
Hemodynamic instability (SBP <80 mmHg, HR >130 bpm)
Fever >39 °C or chills
WBC >18,000/mm^3
Presence of peritonitis on P/E
Palpable inflammatory RUQ mass
Diastase (amylase) >200 (normal 20–100)
Bilirubin >85 μmol/L (5 times the norm)
Multiorgan failure

SBP systolic blood pressure, *HR* heart rate, *RUQ* right upper quadrant, *WBC* white blood cells, *NL* normal limit, *P/E* physical examination, *NYHA* New York Heart Association

[a] Any one is a ground for exclusion

pre-admission medications were continued except for oral hypoglycemic drugs. All patients were administered a smooth muscle relaxant (papaverine, smooth muscle relaxant, 80 mg every 8 h) and gastric acid-reducing medications including H_2 blockers or proton pump inhibitors. Analgesics were ordered as needed and included dipyrone (IV/PO, 1 g every 4–6 h), morphine (IV, 0.1 mg/kg every 4–6 h), meperidine (IM 50–75 mg every 12 h), etodolac (PO 400–600 mg every 12 h), or tramadol (IV/PO 50–100 mg every 4–6 h).

Group A (intravenous antibiotic treatment) was treated with amoxicillin clavulanate (Augmentin) (1 g IV every 8 h) until discharge. Patients allergic to penicillin ($n = 12$) were treated with a combination of ciprofloxacin (400 mg IV every 12 h) and metronidazole (500 mg IV every 8 h).

Pharmacy constraints made it impossible to perform a double-blind, placebo-controlled study.

Criteria for protocol interruption

Patients in the nonantibiotic treatment group were started on intravenous antibiotic treatment for one of the following reasons.

1. Lack of clinical improvement within 72 h of admission.
2. Clinical deterioration, determined by the development of peritoneal irritation signs, hemodynamic instability, or rising fever >39 °C.
3. Laboratory deterioration, determined by the WBC count rising above 18,000/mm^3, bilirubin rising to >85 μmol/L, or amylase rising to >200 U/L.
4. Radiological deterioration, determined by gallbladder wall thickening of >8 mm.

[Repeated laboratory and radiology studies (sonography) were performed in accordance at the attending surgeon's discretion.]

Patients who failed to improve or deteriorated under conservative management with antibiotic treatment were treated with percutaneous cholecystostomy tube placement. Patients with a second episode of ACC, requiring a second admission, were treated with intravenous antibiotics regardless of their initial randomization group.

Objectives

The primary endpoints were the length of hospital stay (LOS) at the index admission and the combined length of stay for all subsequent admissions including elective admission for cholecystectomy for both groups. Secondary endpoints included the time interval to pain resolution, time interval to resumption of oral (liquid) intake, the need for percutaneous tube (PCT) placement, number of readmissions for relapse of ACC, operating time, and postoperative complications.

Safety was determined by assessing the above endpoints and any other adverse events during the study. Complications were evaluated using a severity scale developed at our department [16]. Interim analysis was performed every 6 months to identify significant differences between the groups and to document adverse events.

Outcome

The following data were collected and recorded: demographic data, co-morbidities, number of days with symptoms prior to admission. On admission, we recorded the temperature and heart rate, performed a physical examination (by a surgeon), and obtained laboratory values and sonographic findings of the gallbladder. Once admitted, the patients' follow-up included routine vital signs, visual analog score (VAS) grading of pain, use and dosage of analgesics, and repeated daily physical examination findings. Other data included the need for a PCT, hospital LOS, time to resumption of oral intake, repeated laboratory values, detailed recurrent episodes, and time interval until delayed laparoscopic cholecystectomy (LC), bile cultures, operative details, and postoperative complications. All outcomes were prespecified and were detailed at the study's protocol prior to trial initiation. There were no changes of trial outcomes after the trial commenced.

Sample size

Sample size calculation was based on outcome data of patients admitted to our institution for ACC between January 2005 and December 2006. A total of 164 charts were reviewed, identifying 118 patients who met the inclusion criteria. All patients were treated with intravenous antibiotics combined with supportive care resulting in a mean LOS of 4.0 ± 1.6 days.

As the primary endpoint was hospital LOS, the study group of supportive care only without intravenous antibiotic therapy could be considered equivalent if the LOS difference between the mean LOS of the two study groups did not exceed 1 day ($M = 1$; 25 %). Based on the past 2 years' average LOS with its standard deviation, noninferiority would be assumed with a power of 80 % and significance of 5 % with a sample size of 39 patients per group.

Randomization

Randomization (in a 1:1 ratio) was stratified in blocks of 10 using a computerized random number generator list. Once a patient was admitted, met all the inclusion criteria, and consented to participate in the study, a study number and group assignment for the patient were obtained by placing a telephone call to the study coordinator who was blinded to the patient's details. After randomization, the patient and the staff members were made aware of the participation of the patient in the study and the assigned treatment group.

Statistical methods

Summary statistics were performed using established methods. Continuous variables are presented as the mean ± standard error of mean (SEM). The categoric variables between groups were compared using Fisher exact test or χ^2 test, as appropriate. Associations between categoric factors were studied with Fisher's exact test or the χ^2 test, as appropriate. Association between non-categorical (continuous) variables was performed using Student's t test. SPSS statistical package version 17.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Two sided $p < 0.05$ was regarded as being statistically significant.

Results

Patient characteristics

Between February 2008 and February 2010, a total of 215 patients were admitted through the emergency room with the diagnosis of ACC. Among them, 90 patients did not meet inclusion criteria because of age >70 years ($n = 44$), concomitant choledocholithiasis or pancreatitis ($n = 21$), or not meeting the radiology criteria ($n = 11$). In all, 23 patients did meet the inclusion criteria but were not offered participation in the study by rotating interns or residents unaware of the ongoing study, and 18 patients elected not to participate (Fig. 1). A total of 84 patients were enrolled in the study and were randomly assigned to the intravenous antibiotic treatment arm (group A, $n = 42$) and to the nonantibiotic treatment group (group B, $n = 42$). The two study groups did not differ significantly in terms of sex, age, origin, or number of co-morbidities (Table 2).

Index admission

Clinical presentation, laboratory values, and ultrasonography (US) findings are summarized in Table 2. On average, patients in both groups exhibited normal body temperature on admission (36.7 ± 0.1 vs. 36.4 ± 0.1 °C, $p = 0.04$). Patients in the nonantibiotic group had a trend toward a thicker gallbladder wall (6.0 ± 0.2 vs. 5.3 ± 0.2 mm, $p = 0.05$) as measured by US. Severe abdominal pain on admission was reported more frequently in the nonantibiotic group (60 vs. 40 %, $p = 0.06$) and this group included more patients with elevated LFT results; however, the difference did not reach statistical significance. Increased tendency for the presence of pericystic fluid accumulation (31 vs. 17 %, $p = 0.12$) was observed in the nonantibiotic group.

Patients in the nonantibiotic group had a significantly longer time interval to oral liquid intake resumption (2.2 ± 0.2 vs. 1.7 ± 0.1 days, $p = 0.02$). Nevertheless, the time interval to regular oral diet intake (2.8 ± 0.2 vs. 3.2 ± 0.2 days, $p = 0.16$) and the overall hospital LOS (3.8 ± 0.2 vs. 3.8 ± 0.3 days, $p = 0.89$) were not significantly different between the two study groups. In the intravenous antibiotic treatment group, five (12 %) patients required PCT placement versus only two (5 %) patients in the nonantibiotic group ($p = 0.43$). Eight (19 %) patients assigned to the nonantibiotic group were crossed over to the antibiotic group.

Readmissions

The mean follow-up for the entire cohort was 17.1 months (range 4–28 months); it was 16.4 ± 5.0 months in the antibiotic group versus 17.7 ± 6.0 months in the nonantibiotic group ($p = 0.49$). A long follow-up was performed to record repeat episodes in those patients who elected not to undergo surgery. Of the entire cohort, 10 patients (11.4 %) were readmitted to the hospital for recurrent biliary disease. Six (19 %) patients in the antibiotic

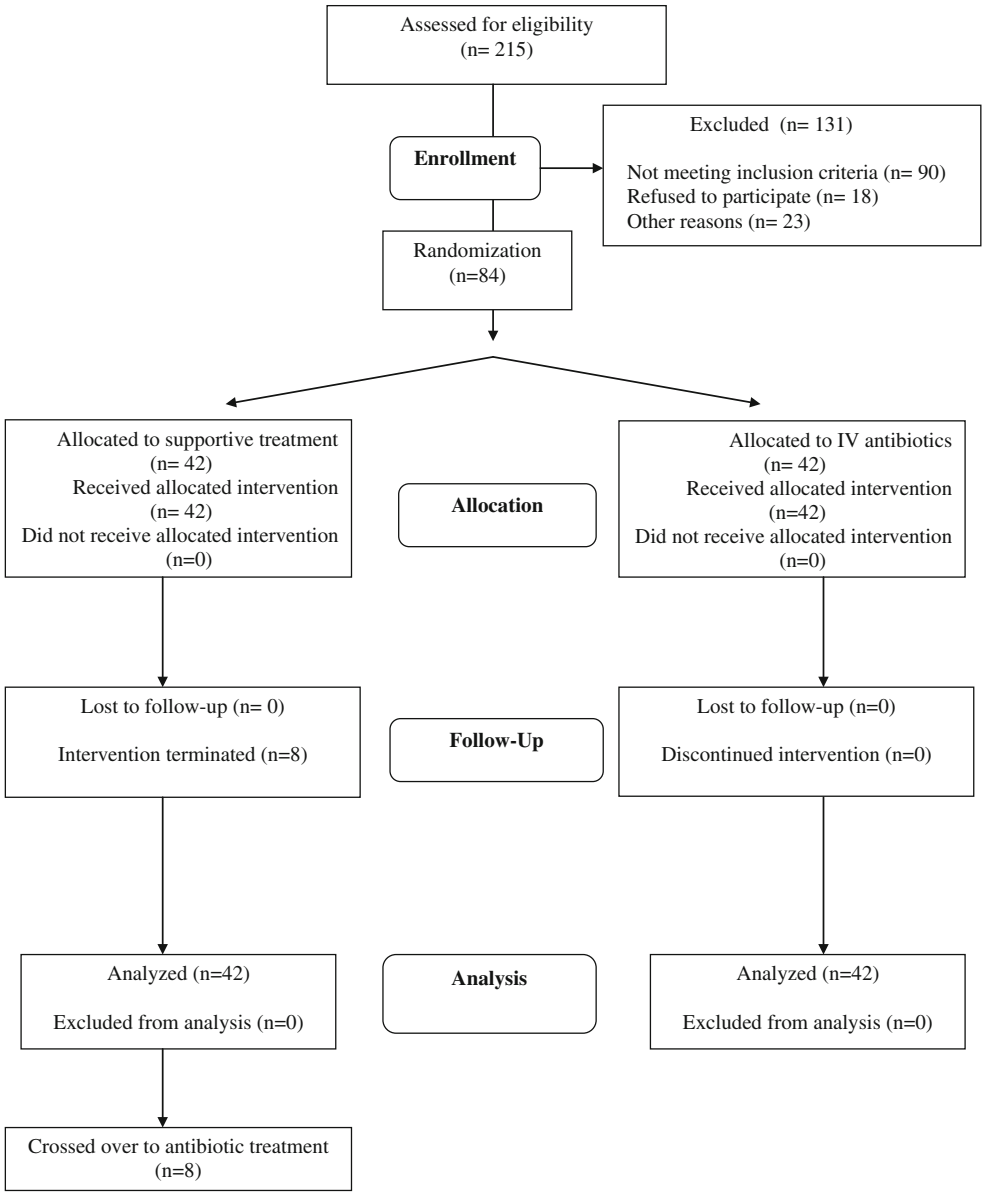

Fig. 1 Study flow chart

treatment group were readmitted versus four (13 %) in the nonantibiotic group ($p = 0.73$). In the intravenous antibiotic treatment group, the mean time to recurrent admission was 29 days (range 3–112 days). Two patients were admitted for a simple biliary colic episode and four for recurrent ACC. The mean hospital LOS of all six patients during their second admission was 3.8 days (range 1–6 days), and none required PCT placement. Five of these six patients subsequently underwent uncomplicated delayed LC. Of the nonantibiotic treatment group, four patients (13 %) were readmitted, with a mean time to readmission of 14 days (range 3–36 days). One patient was admitted for a simple biliary colic episode, one patient for gallstone pancreatitis, and two patients for recurrent ACC. The mean LOS of all four patients was 4.5 days (range 1–8 days), and one patient required PCT placement during this second admission. Only two patients underwent uncomplicated delayed LC. One of the two patients who chose to forego surgery was found to be pregnant during her second admission and has not had surgery up to now. No patients required a third admission for biliary stone disease.

Surgery

All patients were scheduled for elective LC within 6 to 8 weeks after discharge following their first admission. Results of surgery for both groups are summarized in Table 3. More patients opted to undergo surgery in the

Table 2 Patient and disease characteristics on presentation

Variable	Antibiotic Tx ($n = 42$)	No antibiotic Tx ($n = 42$)	p
Demographics			
Age (years)	46.8 (25–65)	44.3 (22–69)	0.37
Male sex	24 (57 %)	22 (52 %)	0.66*
Co-morbidities			
None	25 (60 %)	31 (74 %)	0.37*
≥1	17 (40 %)	11 (26 %)	
Clinical characteristics			
Prior pain (days)	1.7 (0–7)	1.9 (0–7)	0.59
Vital signs			
HR	80 (44–126)	79 (55–127)	0.89
Temperature (°C)	36.4 (35.6–38.2)	36.7 (36.0–38.0)	0.04
Physical examination			
Mild pain	25 (60 %)	17 (40 %)	0.24*
Severe pain	17 (40 %)	25 (60 %)	0.14*
Positive Murphy sign	31 (74 %)	32 (76 %)	0.8*
Laboratory values			
WBC (NL 4.0–10.0 10^9/L)	11.8 (4.4–18)	11.4 (4.4–17)	0.62
Total bilirubin (NL 0–17 μmol/L)	11.9 (2–66)	12.4 (3–72)	0.84
ALT (NL 0–40 U/L)	41 (3–329)	65 (7–764)	0.32
AST (NL 0–35 U/L)	39 (15–151)	70 (11–615)	0.16
GGTP (NL 5–36 U/L)	75 (10–493)	108 (7–1038)	0.43
AlkP (NL 40–130 U/L)	99 (44–328)	100 (52–269)	0.88
Radiology (US) findings			
Stones	40 (95 %)	38 (90 %)	0.86*
Sludge	2 (5 %)	4 (10 %)	0.37*
Wall thickening (mm)	5.3 (4–10)	6.0 (4–12)	0.05
GB diameter	40 (30–62)	39 (22–58)	0.63
Pericystic fluid	7 (17 %)	13 (31 %)	0.12*

Tx treatment, *HR* heart rate/min, *WBC* white blood cells (10^9/L), *ALT* alanine transferase, *AST* aspartate aminotransferase, *GGTP* γ-glutamyl-transferase, *AlkP* alkaline phosphatase, *NL* normal limit, *US* ultrasonography, *GB* gallbladder

Results are given as the mean and range or the number and percent

* χ^2 test

Table 3 Perioperative course

Variable	Antibiotic Tx	No antibiotic Tx	p
Surgery	36 (86 %)	26 (62 %)	0.02
Time from discharge to surgery (days)	58 (17–156)	55 (17–240)	0.75
OR time (minutes)	71 (26–205)	61 (22–116)	0.23
Drain placement	11 (30 %)	5 (19 %)	0.38
Positive bile cultures	8 (22 %)	3 (12 %)	0.5
Complications	0	2 (7.7 %)	0.16
LOS (days)	1.4 (1–3)	1.4 (1–6)	0.83

OR operating room, *LOS* length of stay in hospital

Results are the mean and range or the number and percent

intravenous antibiotic treatment group than in the nonantibiotic treatment group (86 vs. 62 %, $p = 0.02$). The mean operating time and the mean LOS were not significantly different between the two study arms. The rate of postoperative complications was higher in the nonantibiotic treatment group (0 vs. 2, 7.7 %; $p = 0.16$). Major complications (grades III–IV) included one patient who required reoperation for bleeding and another who required

endoscopic retrograde cholangiopancreatography (ERCP) for sludge evacuation from the common bile duct. There were no conversions to open surgery, no bile duct injuries, and no postoperative bile leak in either group. Bile cultures were sent for all patients who underwent surgery. Cultures were positive in eight (22 %) patients (*Escherichia coli* in six and *Klebsiella pneumoniae* in two) in the antibiotic group versus three (12 %) patients (*E. coli*) in the nonantibiotic group ($p = 0.5$).

Length of stay

There was no significant difference between the groups regarding the LOS during the index admissions, any second admissions (3.8 ± 0.7 vs. 4.5 ± 1.2 days, $p = 0.67$), or admissions for surgery (Table 3). The overall mean LOS was calculated as the sum of all admissions; it was longer for the antibiotic treatment group (5.6 ± 0.3 vs. 5.1 ± 0.4 days, $p = 0.29$), but the difference was not statistically significant.

Crossover patients

Eight patients who were initially randomized to the nonantibiotic treatment group were crossed over to intravenous antibiotic treatment during their index admission. Details of these patients are presented in Table 4. To identify risk factors for failure of the nonantibiotic approach, we compared the patients who crossed over to antibiotic treatment to those who did not. The comparison is presented in Table 5. After Bonferonni correction for multiple comparisons, the only variables that remained significant were the longer time to liquid and oral diet (3.6 ± 0.4 vs. 1.9 ± 0.2 days and 4.8 ± 0.4 vs. 2.8 ± 0.2 days, respectively) and overall longer hospital LOS (6.3 ± 0.8 vs. 3.3 ± 0.2 days) for the crossover patients.

Discussion

The treatment of mild ACC with intravenous antibiotics is widely accepted and practiced. The Surgical Infection Society and the Infectious Diseases Society of America adopted this approach despite the lack of scientific evidence [12].

In this prospective randomly controlled trial, the addition of intravenous antibiotic treatment to supportive care had limited, if any, effect in patients with mild ACC. The only measurable impact of intravenous antibiotics was a reduction of the time interval to liquid diet intake by half a day. Otherwise, the disease course was not significantly different between the groups, and even the delayed surgical outcome was comparable. Most importantly, the LOS during the index admission, admission for surgery, and total LOS was much the same for both study groups.

In the present study, patients initially treated by supportive care only, with no antibiotics, and who were crossed over to intravenous antibiotic treatment are a subgroup of special interest. These patients took longer to return to liquid and oral diet, required more cholecystostomy tube placement, and ended up having a longer LOS. These differences, however, did not result in any differences during the admission for surgery. An attempt to identify such patients based on their clinical presentation did not reveal any predicting factors differentiating them from the other patients in the nonantibiotic group. However, to avoid harm to the study patients, we exercised a low threshold for crossover in the nonantibiotic group so that some of these patients might have been able to complete their admission with no antibiotic treatment regardless of their more prolonged course.

One disadvantage of delayed cholecystectomy is the rate of readmissions between the index admission and until when surgery is performed 4 to 6 weeks later. Six (19 %)

Table 4 Characteristics of patients requiring crossover from no-antibiotic group to intravenous antibiotics

Patient	Age (years)	Sex	Admission day crossover	Documented reason for crossover	Index admission LOS	Cholecystostomy tube (admission day)	Second admission LOS (days)
T.S.	37	F	1	Increasing abdominal pain	3	–	8
A.T.	29	M	1	Increasing abdominal pain and elevated WBC	6	–	–
A.S.	55	M	2	Increasing abdominal pain and increased T to 37.9 °C	5	–	–
K.R.	58	F	2	Increasing abdominal pain	5	Yes (day 2)	–
J.N.	69	F	3	Elevated LFTs	7	–	–
S.H.	53	F	2	Lack of improvement	7	Yes (day 4)	–
M.Z.	64	F	3	Lack of improvement	11	–	–
B.B.	59	M	3	Lack of improvement	6	–	–

F female, *M* male, *T* temperature, *LFTs* liver function tests

Table 5 Patients treated without antibiotics compared to those who crossed over to antibiotic treatment

Variable	Completed hospitalization with no antibiotic Tx ($n = 34$)	Crossed over to antibiotic Tx ($n = 8$)	p
Demographics			
Age (years)	42.0 ± 2.3	52.0 ± 4.7	0.05
Female sex	44 %	63 %	0.44*
Co-morbidities (≥1)	26 %	25 %	0.86*
Clinical characteristics			
Prior pain (days)	1.9 ± 0.3	2.0 ± 0.5	0.86
Physical examination			
HR (bpm)	77.0 ± 2.8	86.0 ± 5.1	0.17
Temperature (°C)	36.6 ± 0.1	37.0 ± 0.3	0.09
Positive Murphy sign	75 %	77 %	1.0*
Laboratory values and radiology findings			
WBC (10^9/L); (NL 4.0–10.0 10^9/L)	11.3 ± 0.5	11.8 ± 1.5	0.70
GB wall thickening (mm)	5.9 ± 0.3	6.1 ± 0.4	0.73
Pericystic fluid	27 %	50 %	0.22*
GB diameter (mm)	40 ± 1.6	37.0 ± 1.7	0.52
Hospital course (days)			
Time to liquid intake	1.9 ± 0.2	3.6 ± 0.4	<0.0005
Time to oral intake	2.8 ± 0.2	4.8 ± 0.4	<0.0005
Hospital stay	3.3 ± 0.2	6.3 ± 0.8	<0.0005
PCT placement	0	25 %	0.03*
Readmission	12.5 %	8.8 %	1.0*
LOS following cholecystectomy (days)	1.4 ± 0.2	1.5 ± 0.4	0.88
OR time (min)	63.0 ± 3.9	55.0 ± 7.9	0.55
Complication rate	9 %	0	1.0*

PCT percutaneous cholecystostomy tube

Results are the mean

* χ^2 test

patients in the antibiotic treatment group required readmission for a mean hospital stay of 3.8 days—well within the range of readmission rate reported in the literature [17, 18]. The patients in the nonantibiotic group had a lower rate of readmissions: four (13 %) patients with a mean hospital stay of 4.5 days; this difference was statistically nonsignificant. Despite prolonging the overall LOS, these patients, in both groups, did not have surgical complications. Another disadvantage of the delayed approach is patients foregoing surgery [18–20]. In this study, 86 % of the patients in the antibiotic group and only 62 % in the nonantibiotic group had their gallbladder removed, although all patients were uniformly scheduled for surgery on discharge from their index admission.

The hypothesis at the base of our study was that mild cholecystitis is an inflammatory process rather than an infectious one. The reported incidence of bactibilia has a wide range, and only purely descriptive studies are available [8, 21–28]. Obviously, cultures from cholecystostomy tubes are irrelevant, as no mild cases of acute cholecystitis require such an intervention. Studies including patients with choledocholithiasis [8, 21–24] are also unreliable, as the rate of bactibilia is much higher in patients with cholangitis than in those with acute cholecystitis. The rate of positive bile cultures during surgery varies in accordance with disease severity and ranges between 31 and 72 % [27, 28]. In this study, a relatively low rate of positive intraoperative bile cultures was identified, with only eight (22 %) patients in the antibiotic treatment group and only three (12 %) patients in the nonantibiotic group (Table 3). This may support our hypothesis that mild acute cholecystitis is associated with a low infection rate. The trend toward a lower rate of positive cultures in the nonantibiotic group suggests that antibiotic usage does result in bacterial overgrowth, although the difference between the groups did not reach statistical significance. Moreover, the presence of bactibilia does not, by definition, require antibiotic treatment—as is also the case in patients with biliary stents.

The most recent recommendations by the Surgical Infection Society and the Infectious Diseases Society of America include intravenous antibiotics as part of the treatment of acute cholecystitis [12]. This recommendation is based mainly on the Tokyo consensus meeting results and guidelines [9, 15] and a comprehensive review of the management of acute calculus cholecystitis by Strasberg [3]. The Tokyo guidelines do not clearly state the evidence supporting their recommendations for antibiotic treatment in patients with acute calculus cholecystitis. The recommendation appears to be based on seven studies reporting the rate of bactibilia in patients with various biliary inflammatory conditions [8, 21–26], five of which published by the same group [8, 21, 23, 24, 26]. Not a single study has investigated the need for antibiotic treatment in acute calculus cholecystitis. Nevertheless, the recommendation for antibiotic treatment is graded as A [9]. In 2008, in a comprehensive review, Strasberg [3] supported his recommendation for antibiotic therapy of acute calculus cholecystitis based on the Tokyo guidelines, the Surgical Infection Society recommendation from 2003 [29], and two studies demonstrating the presence of bactibilia [27, 28]. Thus, the conclusive recommendation for antibiotic treatment in all patients with acute cholecystitis seems to rely on limited scientific evidence [10, 11]. Mild acute cholecystitis is identified by the Tokyo guidelines as a distinct entity that may be even treated with oral antibiotics and

NSAIDs or observed without antibiotics at all [9]. This recommendation, suggesting an inflammatory process rather than infection, also lacks convincing scientific support. It was thus tested in the current study.

Several limitations should be noted. No patients with moderate or severe cholecystitis were included. Hence, no recommendations can be made for these subgroups. Subjective clinical decision-making poses another important limitation as potential bias. Decisions on the need for a cholecystostomy tube were tailored to each patient's status and depended on both objective parameters and the surgeon's evaluation. In contrast, patients were discharged once oral diet was resumed, and so clinical judgment had limited effect on the LOS. Such limitations exist in any trial that involves patient care based on physicians' evaluations. Lastly, this trial was not performed as a blinded study due to limitations cast by our pharmacy. Although the number of patients enrolled may appear to be low, it did exceed the number based on sample size calculations. The strengths of our study include the fact that it was a prospective randomized controlled trial and is the first study that addresses the role of antibiotic treatment in mild acute calculus cholecystitis. The two study groups did not differ in their demographics or clinical presentation; and all patients were followed until surgery was performed (or for a longer period of time if they elected not to undergo surgery) to assess readmission rates and differences in surgical outcome. The study was not designed to evaluate other management aspects, such as cessation of oral diet or delayed cholecystectomy, and no conclusions should be made regarding these aspects.

Conclusions

We presented the first randomized controlled trial investigating the role of intravenous antibiotic treatment in patients with mild acute calculus cholecystitis. Avoiding antibiotic treatment did not affect the overall LOS, the number of readmissions, or the surgical outcome. On the basis of these findings, we suggest that some patients with mild acute cholecystitis may be managed without antibiotic treatment. Careful supervision is required to identify a small subgroup of patients with a more acutely progressing disease requiring the addition of intravenous antibiotics during their hospital course.

References

1. Browning JD, Horton JD (2003) Gallstone disease and its complications. Semin Gastrointest Dis 14:165–177
2. Shaffer EA (2006) Gallstone disease: epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol 20:981–996
3. Strasberg SM (2008) Clinical practice: acute calculous cholecystitis. N Engl J Med 358:2804–2811
4. Ziessman HA (2003) Acute cholecystitis, biliary obstruction, and biliary leakage. Semin Nucl Med 33:279–296
5. Lemos R, Franca PH, Ferreira LE et al (2010) Detection of bacterial DNA in acute and chronic cholecystitis. Br J Surg 97:532–536
6. Galili O, Eldar S Jr, Matter I et al (2008) The effect of bactibilia on the course and outcome of laparoscopic cholecystectomy. Eur J Clin Microbiol Infect Dis 27:797–803
7. Thompson JE Jr, Bennion RS, Doty JE et al (1990) Predictive factors for bactibilia in acute cholecystitis. Arch Surg 125:261–264
8. Csendes A, Burdiles P, Maluenda F et al (1996) Simultaneous bacteriologic assessment of bile from gallbladder and common bile duct in control subjects and patients with gallstones and common duct stones. Arch Surg 131:389–394
9. Yoshida M, Takada T, Kawarada Y et al (2007) Antimicrobial therapy for acute cholecystitis: Tokyo guidelines. J Hepatobiliary Pancreat Surg 14:83–90
10. Kanafani ZA, Khalife N, Kanj SS et al (2005) Antibiotic use in acute cholecystitis: practice patterns in the absence of evidence-based guidelines. J Infect 51:128–134
11. Kune GA, Burdon JG (1975) Are antibiotics necessary in acute cholecystitis? Med J Aust 2:627–630
12. Solomkin JS, Mazuski JE, Bradley JS et al (2010) Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the surgical infection society and the infectious diseases society of America. Surg Infect (Larchmt) 11:79–109
13. Akriviadis EA, Hatzigavriel M, Kapnias D et al (1997) Treatment of biliary colic with diclofenac: a randomized, double-blind, placebo-controlled study. Gastroenterology 113:225–231
14. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med 8:18
15. Mayumi T, Takada T, Kawarada Y et al (2007) Results of the Tokyo consensus meeting Tokyo guidelines. J Hepatobiliary Pancreat Surg 14:114–121
16. Mazeh H, Samet Y, Abu-Wasel B et al (2009) Application of a novel severity grading system for surgical complications after colorectal resection. J Am Coll Surg 208:355–361
17. Gurusamy K, Samraj K, Gluud C et al (2010) Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg 97:141–150
18. Lau H, Lo CY, Patil NG et al (2006) Early versus delayed-interval laparoscopic cholecystectomy for acute cholecystitis: a metaanalysis. Surg Endosc 20:82–87
19. Gurusamy KS, Samraj K (2006) Early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Cochrane Database Syst Rev 4:CD005440
20. Cameron IC, Chadwick C, Phillips J et al (2004) Management of acute cholecystitis in UK hospitals: time for a change. Postgrad Med J 80:292–294
21. Maluenda F, Csendes A, Burdiles P et al (1989) Bacteriological study of choledochal bile in patients with common bile duct stones, with or without acute suppurative cholangitis. Hepatogastroenterology 36:132–135
22. Chang WT, Lee KT, Wang SR et al (2002) Bacteriology and antimicrobial susceptibility in biliary tract disease: an audit of 10-year's experience. Kaohsiung J Med Sci 18:221–228
23. Csendes A, Mitru N, Maluenda F et al (1996) Counts of bacteria and pyocites of choledochal bile in controls and in patients with gallstones or common bile duct stones with or without acute cholangitis. Hepatogastroenterology 43:800–806

24. Csendes A, Becerra M, Burdiles P et al (1994) Bacteriological studies of bile from the gallbladder in patients with carcinoma of the gallbladder, cholelithiasis, common bile duct stones and no gallstones disease. Eur J Surg 160:363–367
25. Kune GA, Schutz E (1974) Bacteria in the billary tract: a study of their frequency and type. Med J Aust 1:255–258
26. Csendes A, Fernandez M, Uribe P (1975) Bacteriology of the gallbladder bile in normal subjects. Am J Surg 129:629–631
27. Jarvinen H, Renkonen OV, Palmu A (1978) Antibiotics in acute cholecystitis. Ann Clin Res 10:247–251
28. Claesson B, Holmlund D, Matzsch T (1984) Biliary microflora in acute cholecystitis and the clinical implications. Acta Chir Scand 150:229–237
29. Solomkin JS, Mazuski JE, Baron EJ et al (2003) Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. Clin Infect Dis 37:997–1005